

**Figure S1. Consort diagram depicting overall study design, Related to Figure 1**

All patients were recruited from QECH in Blantyre, Malawi. Patients were lost due to declined enrollment, failure to meet inclusion requirements, and/or an alternative diagnosis following enrollment. Patients with low parasite burden (unable to accurately assess *var* transcript levels) and no MRI evaluation were excluded from the machine learning models.

**Figure S2. Transcript profiling of *var* genes with second generation primers, Related to Figures 2 and 3**

EPCR-binding CIDR $\alpha$ 1.1/4/5/6/7/8 containing *var* transcripts are present at high levels in Ret+CM cases across the brain swelling spectrum and fatal cases compared to UM cases. P-values correspond to Kruskal-Wallis adjusted for multiple comparisons using Dunn's correction.

**Figure S3. Machine learning retinopathy and swelling models, Related to Figure 4**

Host and parasite factors that discriminate patients with retinopathy and severe swelling in a RF analysis after Pfhrp2 filtration. Summary of the four RF models: Ret+CM versus UM, Ret+CM versus Ret-CM, severe swelling versus UM, and severe swelling versus absence of swelling.

**Figure S4. Overview of next-generation sequencing methodology and classification of DBL $\alpha$  tags by BLAST analysis of a custom database of *var* genes, Related to Figure 5**

(A) Steps involved in preparation of Illumina MiSeq libraries. Gel purification steps are omitted for simplicity.

(B) Computational analyses of Illumina MiSeq reads.

(C) BLAST strategy for classifying NGS DBL $\alpha$  tags into different PfEMP1 types.

(D) Designation of PfEMP1 type to DBL $\alpha$  tags based on BLAST analysis. Bar graph shows the proportional representation of unique DBL $\alpha$  sequence reads in each patient. Unique tags have been colored based on their BLAST identity to 521 *var* sequences. Classification predictions were based on the top 5 hits of BLAST searches performed on a custom library of near full length PfEMP1 sequences from Rask et al. and Jespersen et al. Dark color:  $\geq 4$  of the top 5 hits were of the same type. Light color: 3 of the top 5 hits were of the same type. Ambiguous:  $< 3$  were of the same type. See also Table S7.

**Figure S5: Binding specificity of 62B1-1-CIDR $\alpha$ 1.7 and IT4var31-CIDR $\alpha$ 4 binding for CHO745-EPCR and CHO745-CD36 cells, Related to Figure 6**

- (A) Binding of 62B1-1-CIDR $\alpha$ 1.7 to CHO745-EPCR cells, but not CHO745 or CHO745-CD36 cells.
- (B) Binding of IT4var31-CIDR $\alpha$ 4 to CHO745-CD36 cells, but not CHO745 or CHO745-EPCR cells.

Binding was assessed by flow cytometry. Mean  $\pm$  SD. A representative graph is shown of n=3 independent experiments. Binding to the negative control cells is shown only for 50  $\mu$ g/ml.

**Figure S6: Summary illustration of host and parasite factors important for CM**

## **disease progression, Related to Figures 1-6**

Visual depiction of host and parasite factors distinguishing CM (i.e. Ret+CM + severe swelling and/or fatality) from UM. The inset illustrates how an EPCR-binding CIDR $\alpha$ 1.7 domain isolated from the brain of a fatal pediatric CM case may impair the APC-EPCR protective pathway by inhibiting protein C activation or by preventing the interaction between soluble APC and EPCR.

**Table S1.** Summary of patient details and *P. falciparum var* transcript analysis, Related to Figure 1 and Table 1

**Table S2.** Clinical characteristics of patients excluded from *var* expression analysis, Related to Table 1

**Table S3.** Primer sequences for qRT-PCR targets, Related to Figures 2-3 and S2

**Table S4.** *var* domain expression levels in Ret+CM, Ret-CM, and UM cases, Related to Figures 2 and 3

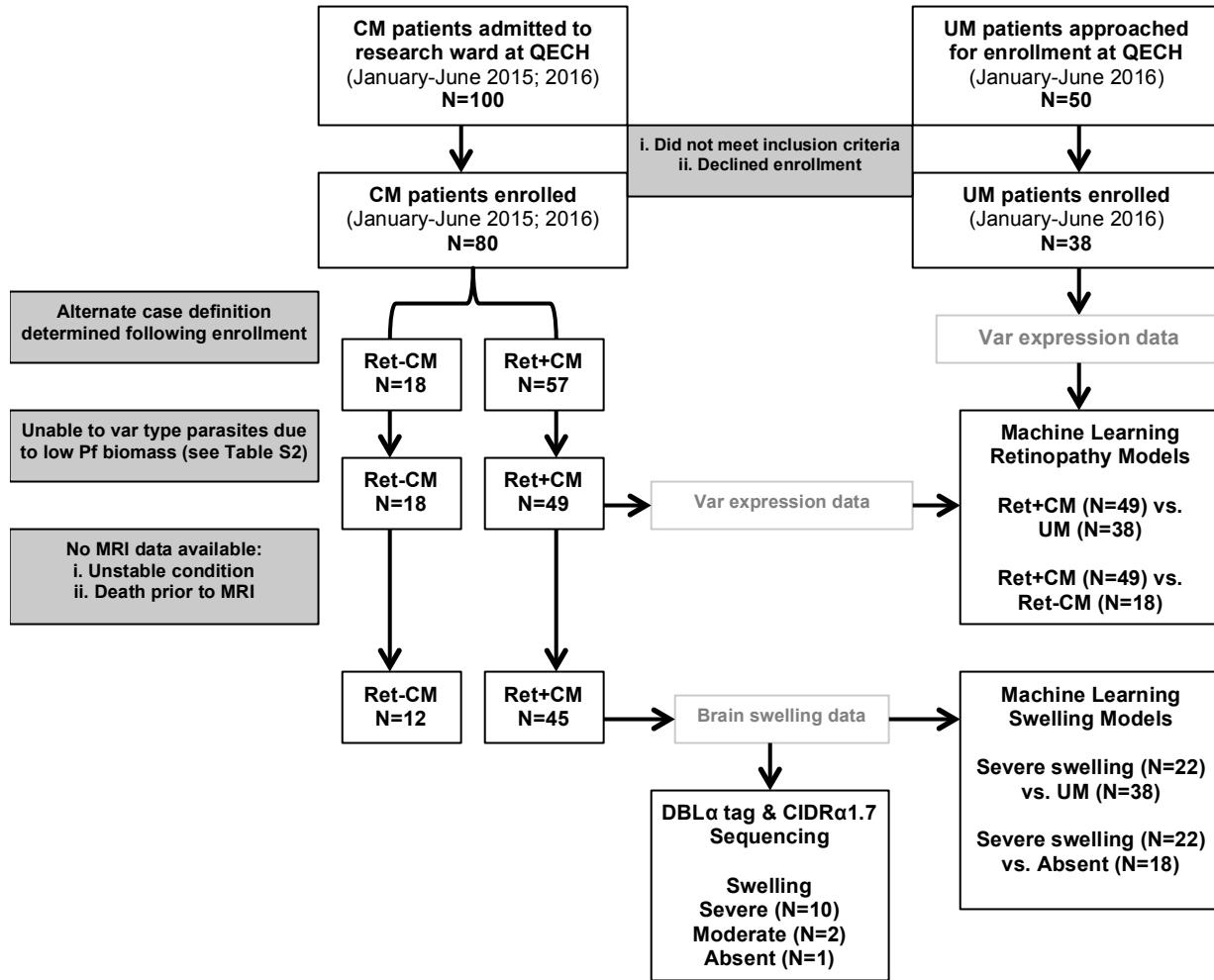
**Table S5.** *var* domain expression levels in CM cases by brain volume/swelling severity, Related to Figure 3

**Table S6.** Primer grouping for set enrichment analysis, Related to Figure 4

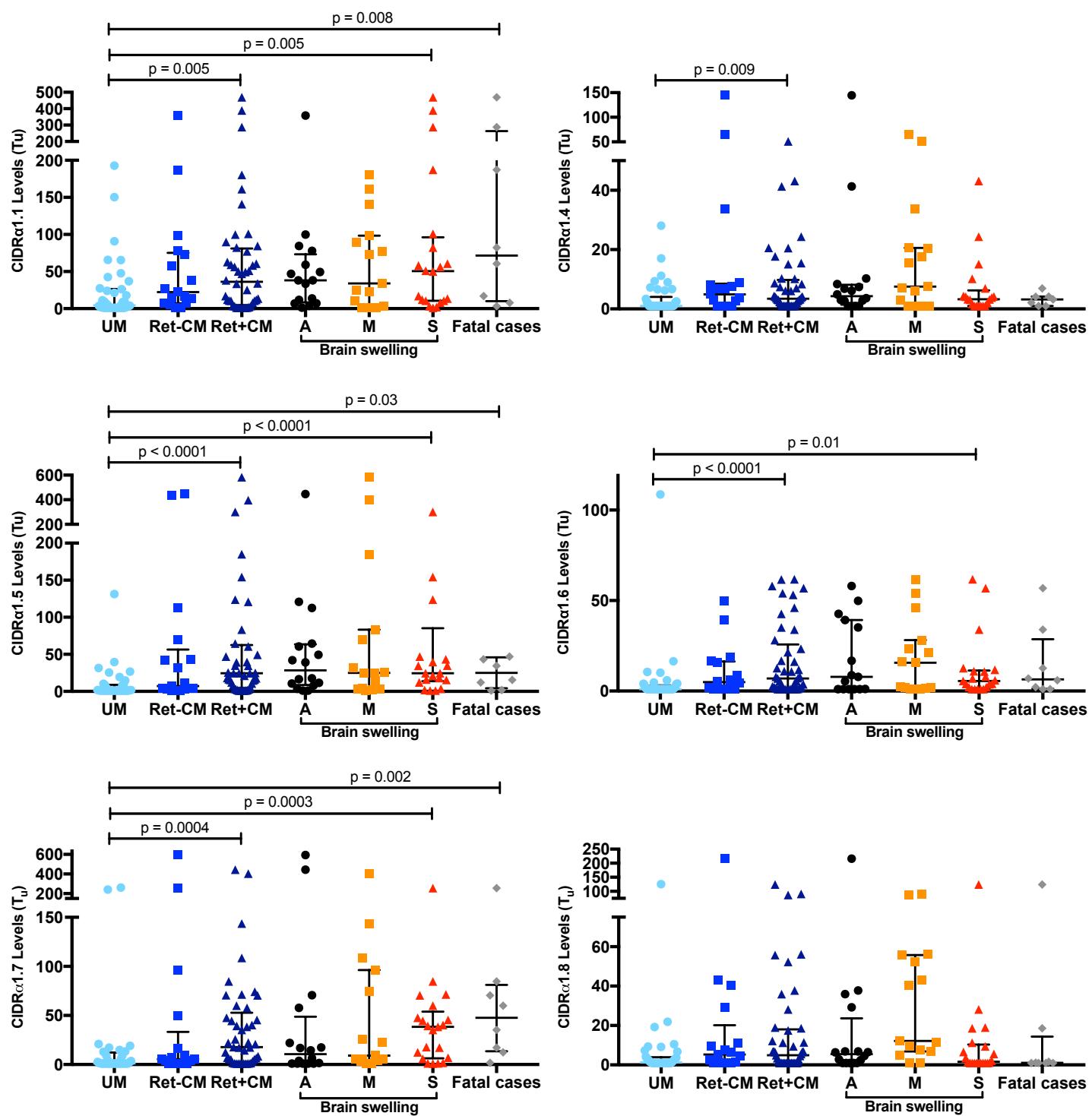
**Table S8.** Number of unique DBL $\alpha$  tags per patient, Related to Figure 5

**Table S9.** Summary of identical DBL $\alpha$  tags in/between 2015-2016 isolates and 1999-2003 brain samples, Related to Figure 5

**Figure S1**

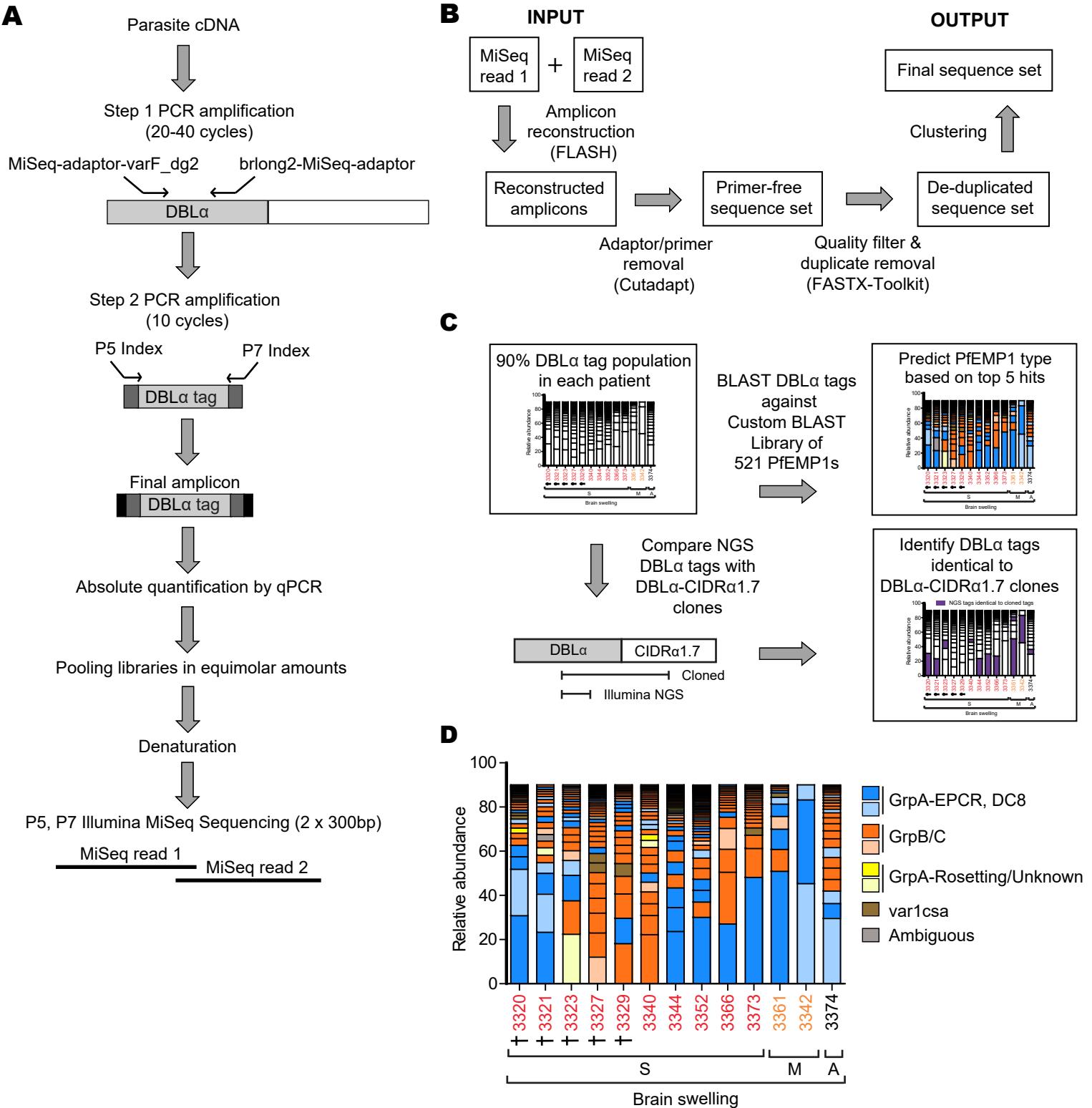


**Figure S2**

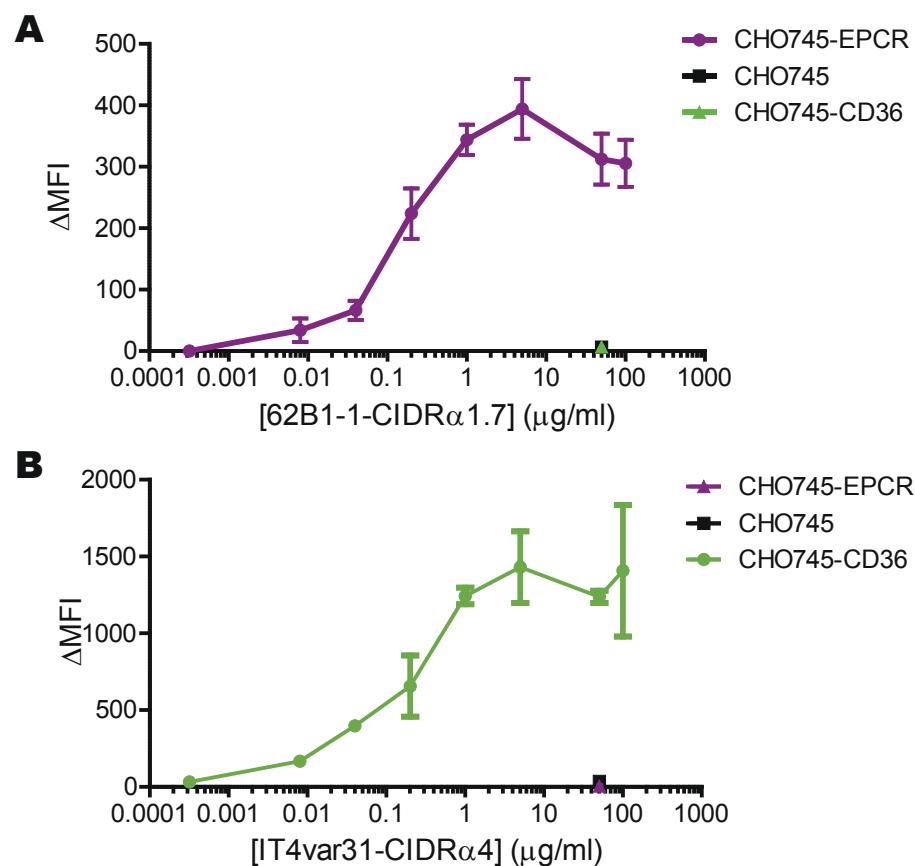


## Figure S3

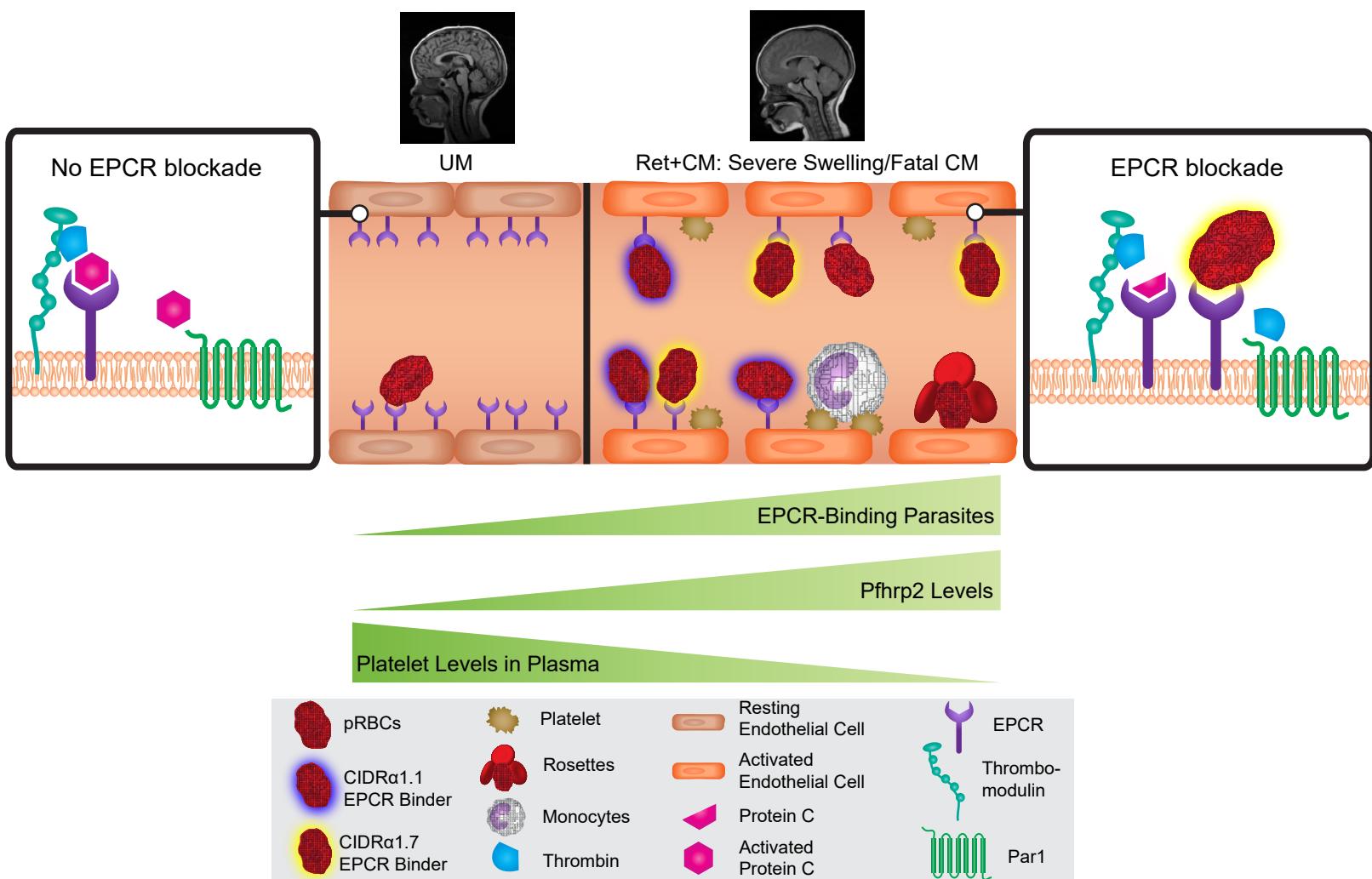
**Figure S4**



**Figure S5**



**Figure S6**



**Table S1**
**Table S1. Summary of patient details and *P. falciparum* var transcriptional analysis, Related to Figure 1 and Table 1**

Patient ID	Age (yr)	Clinical Presentation	MRI Score	Severe Swelling	Severe Anemia	Respiratory Distress	Neurocognitive Sequelae	Death	qRT-PCR (Y/N)	DBLa-CIDRa1.7 clone	NGS DBLa
MI043	2	UM	UD	UD	N	N			Y		
MI044	8	UM	UD	UD	N	N			Y		
MI045	11	UM	UD	UD	N	N			Y		
MI046	1	UM	UD	UD	N	N			Y		
MI047	2	UM	UD	UD	N	N			Y		
MI048	5	UM	UD	UD	N	N			Y		
MI049	8	UM	UD	UD	N	N			Y		
MI050	6	UM	UD	UD	N	N			Y		
MI051	10	UM	UD	UD	N	N			Y		
MI052	4	UM	UD	UD	N	N			Y		
MI053	1	UM	UD	UD	N	N			Y		
MI054	2	UM	UD	UD	N	N			Y		
MI055	10	UM	UD	UD	N	N			Y		
MI056	7	UM	UD	UD	N	N			Y		
MI057	6	UM	UD	UD	N	N			Y		
MI058	6	UM	UD	UD	N	N			Y		
MI059	11	UM	UD	UD	N	N			Y		
MI060	1	UM	UD	UD	N	N			Y		
MI061	2	UM	UD	UD	N	N			Y		
MI062	10	UM	UD	UD	N	N			Y		
MI063	3	UM	UD	UD	N	N			Y		
MI064	2	UM	UD	UD	N	N			Y		
MI065	11	UM	UD	UD	N	N			Y		
MI066	4	UM	UD	UD	N	N			Y		
MI067	4	UM	UD	UD	N	N			Y		
MI068	4	UM	UD	UD	N	N			Y		
MI069	7	UM	UD	UD	N	N			Y		
MI070	3	UM	UD	UD	N	N			Y		
MI071	6	UM	UD	UD	N	N			Y		
MI072	1	UM	UD	UD	N	N			Y		
MI073	7	UM	UD	UD	N	N			Y		
MI074	6	UM	UD	UD	N	N			Y		
MI075	7	UM	UD	UD	N	N			Y		
MI076	1	UM	UD	UD	N	N			Y		
MI077	6	UM	UD	UD	N	N			Y		
MI078	2	UM	UD	UD	N	N			Y		
MI079	6	UM	UD	UD	N	N			Y		
MI080	2	UM	UD	UD	N	N			Y		
MP3288	2	Ret+CM	2	0	N	N			Y		
MP3288	5	Ret+CM			N	N			Y		
MP3289	1	other			N	Y			Y		
MP3300	1	Ret+CM	8	1	Y	N		died	Y*		
MP3301	3	Ret+CM			N	Y			Y		
MP3302	3	other	6	0	N	Y			Y		
MP3303	1	other	5	0	N	N			Y		
MP3304	1	Ret+CM	3	0	N	N			Y		
MP3305	4	Ret+CM	4	0	Y	N			Y		
MP3306	5	Ret+CM			N	N			Y		
MP3307	2	other			N	N			Y		
MP3308	1	other			N	N			Y		
MP3309	4	Ret+CM			N	Y	sequelae		Y		
MP3310	5	Ret+CM			N	N			Y		
MP3311	2	Ret+CM	7	1	Y	N			Y		
MP3312	5	Ret+CM	3	0	Y	N			Y		
MP3313	3	Ret+CM	7	1	N	Y			Y		
MP3314		UD			N	N			Y		
MP3315	1	Ret+CM			N	N			Y		
MP3316	4	Ret+CM	4	0	N	N			Y		
MP3317	10	Ret+CM	6	0	N	Y			Y		
MP3318	1	Ret+CM			Y	N			Y		
MP3319	2	Ret+CM			Y	N			Y		
MP3320	6	Ret+CM	7	1	N	N		died	Y		
MP3321	2	Ret+CM	8	1	N	Y		died	Y		
MP3322	6	Ret+CM	4	0	N	N			Y		
MP3323	4	Ret+CM	8	1	Y	Y		died	Y		
MP3324	5	Ret+CM	6	0	Y	N			Y		
MP3325	3	Ret+CM	6	0	N	N			Y		
MP3326	6	Ret+CM	5	0	N	N			Y		
MP3327	5	Ret+CM	8	1	N	Y		died	Y		
MP3328	9	Ret+CM	3	0	N	N			Y		
MP3329	8	Ret+CM	8	1	N	N		died	Y		
MP3330	12	Ret+CM	6	0	N	N			Y		
MP3331	3	Ret+CM	4	0	N	Y			Y		
MP3332	6	Ret+CM	4	0	N	Y			Y		
MP3333	2	Ret+CM	5	0	Y	Y	sequelae		Y*		
MP3334	6	Ret+CM	7	1	N	N			Y*		
MP3335	6	Ret+CM			N	N			Y		
MP3336	7	Ret+CM	5	0	N	N			Y		
MP3337	7	Ret+CM	6	0	N	N			Y		
MP3338	9	Ret+CM	6	0	N	N			Y		
MP3339	1	Ret+CM	7	1	Y	N			Y		
MP3340	4	Ret+CM	8	1	N	N			Y		
MP3341	3	Ret+CM	6	0	N	N			Y		
MP3342	4	Ret+CM	6	0	N	N			Y		
MP3343	3	Ret+CM	7	1	N	N			Y		
MP3344	4	Ret+CM	7	1	Y	N			Y		
MP3345	5	Ret+CM	3	0	N	N			Y		
MP3346	2	Ret+CM	7	1	Y	N			Y		
MP3347	5	Ret+CM	7	1	N	N			Y		
MP3348	2	Ret+CM	5	0	N	N			N		
MP3349	4	Ret+CM	3	0	Y	N			Y		
MP3350	7	Ret+CM	4	0	N	Y			Y		
MP3351	7	Ret+CM	4	0	N	N			Y		
MP3352	6	Ret+CM	8	1	N	N			Y		
MP3353	4	Ret+CM	7	1	N	Y			Y		
MP3354	5	Ret+CM	7	1	N	Y		died	Y		
MP3355	3	Ret+CM	6	0	Y	N			Y		
MP3356	1	Ret+CM	5	0	Y	N			Y		
MP3357	1	Ret+CM	6	0	Y	N			Y		
MP3358	2	Ret+CM	8	1	N	Y		died	Y		
MP3359	1	Ret+CM	6	0	N	Y			N		
MP3360	3	Ret+CM	7	1	N	N			N		
MP3361	3	Ret+CM	6	0	N	N			Y		
MP3362	3	Ret+CM	6	0	Y	N			N		
MP3363	7	Ret+CM	8	1	N	N			N		
MP3364	3	Ret+CM	6	0	Y	N			Y		
MP3365	4	Ret+CM	4	0	N	N			N		
MP3366	3	Ret+CM	7	1	N	N			Y		
MP3367	10	Ret+CM	3	0	Y	Y			Y		
MP3368	7	Ret+CM	7	1	N	N			N		
MP3369	4	Ret+CM	6	0	N	Y			N		
MP3370	1	Ret+CM	4	0	N	N			N		
MP3371	7	Ret+CM	1	0	N	Y			Y		
MP3372	1	Ret+CM	4	0	N	N			Y		
MP3373	10	Ret+CM	8	1	N	N			Y		
MP3374	5	Ret+CM	4	0	N	N			Y		
MP3375	3	Ret+CM			Y	Y			Y		
MP3376	1	Ret+CM	7	1	N	N			Y		

UM, uncomplicated malaria; Ret+/Ret+CM, retinopathy positive/negative cerebral malaria; UD, undetermined; Y/N, yes/no; Y\*, only additional CIDRa specific qRT-PCR data available.

MRI score, 1. atrophy 2. mild 3. normal 4. slight swelling 5. mild swelling 6. moderate swelling 7. substantial swelling 8. substantial swelling + effacement & herniation.

Severe swelling, MRI score ≥6; Severe anemia, packed cell volume ≤15%; Respiratory distress, observations of deep breathing, grunting, nasal flaring, chest indrawing, and/or chest retractions.

**Table S2. Characteristics of Ret+CM cases excluded from *var* analysis, Related to Table 1**

Patient Characteristic	<i>var</i> Typed cases (n = 49)	Excluded cases (n = 8)	p-value*
Age (yr), median [IQR]	4.0 [3.0, 5.7]	3.0 [1.5, 5.5]	0.20
Male, n (%)	31 (63.3)	4 (50.0)	0.48
Smear score, median [IQR]	3 [2.0, 4.0]	3 [2.5, 3.5]	0.55
Parasitemia ( $10^3/\mu\text{l}$ ), median [IQR]	3.2 [0.4, 96.3]	21.4 [3.8, 316.1]	0.23
<b>Pfhrp2 (ng/ml), median [IQR]</b>	<b>5196 [1040, 16680]</b>	<b>975 [334, 4447]</b>	<b>0.03</b>
Hgb (g/dL), median [IQR]	7.7 [6.4, 9.0]	7.2 [5.6, 8.8]	0.58
Platelets ( $10^3/\mu\text{l}$ ), median [IQR]	50.0 [32.0, 84.0]	53.5 [29.5, 91.0]	0.89
Total WBC ( $10^3/\mu\text{l}$ ), median [IQR]	8.3 [6.6, 11.6]	10.0 [8.1, 12.5]	0.48
Lactate (mmol/L), median [IQR]	3.4 [2.1, 5.4]	4.7 [2.8, 6.1]	0.40
Blantyre coma score, median [IQR]	2 [1, 2]	1.5 [1, 2]	0.59
Severe malarial anemia, n (%)	17 (34.7)	2 (25.0)	0.59
Respiratory distress, n (%)	11 (22.4)	2 (25.0)	0.87
Jaundice, n (%)	5 (10.2)	0 (0)	0.34
Brain swelling°, n (%)	34 (75.6)	7 (87.5)	0.46
MRI scores (scale 1-8)			
1-4 -- Absence of swelling	11 (24.4)	1 (12.5)	
5-6 -- Mild/moderate swelling	13 (28.9)	4 (50.0)	
7-8 -- Severe swelling	21 (46.7)	3 (37.5)	
Mortality, n (%)	7 (14.3)	0 (0)	0.25

IQR, interquartile range; °*var* typed (n=45), Excluded (n=8); Brain swelling = MRI score > 4.

\*P-values correspond to Wilcoxon rank-sum or chi-squared test.

**Table S3. Primer sequences for qRT-PCR targets, Related to Figures 2-3 and S2**

<b>Primer name</b>	<b>Forward primer(s)</b>	<b>Reverse primer(s)</b>
DBL $\alpha$ 2/α1.1/2/4/7	TCCTACCAATTAGATTACGTCCCTCA	CGTACAATCATATCCATTAAGACTAC
DBL $\alpha$ 1.4	GGTTTCATACTAATGTATGGCATCGTAA	GMACGACTAAAAGACAAGGATTCT
CIDR $\alpha$ 1.4 and CIDR $\alpha$ 1	GGGTTAGAAAATTMTTAATAGACACTA	CTTTTGTTAACCCATYTGTCAAAAC
CIDR $\alpha$ 1.6	AGAAGGCGCAATAAAAGTGTGT	GAATTATTGTCTATGCATCTTCAGC
CIDR $\alpha$ 1.7	CGGAAACTATAACGTGAAAGATAA	CTTTTGTTAACCCATYTGTCAAAAC
DBL $\beta$ 3	TGTRAACAAATMGCACAATTATAAA	GCATCRSCYTTCAAAGCWCTTCT
DBL $\alpha$ -CIDR $\alpha$ DC8	GYTCARAWTATTGCCAACCC	ACCSTYACAWWBAACTACAC
CIDR $\alpha$ 1.1	TAARGTGGGAACATCAACTTAAGAAT	CTAAATCTTYCGAAATTGATCCCCT
DBL $\beta$ 12 and DBL $\beta$ 3/5	CATCAAGTKTGGAGAGCTATGAAATGTG	TAATCTCTATGGGATACCATTACA
DBL $\gamma$ 4/6	AGAAAACAHATTTGCKTGG	CCATGTTCWTTCCACCAGTCDTCAAG
DBL $\alpha$ 1.7	GATTAYGTCCCTCAATTNTAMGWTGGT	GTTTACGAAATGCTTCTCGTTGATTRCC
CIDR $\alpha$ 1.4	AACAATGGAAATGCTATTAYRA	TCGKTTCCCACTTATASTGTC
<b>CIDR<math>\alpha</math>1.1</b>	TGGGAACATCAACTTAAGGATTGCATA TGGGAACATCAACTTAAGAATTGCATA TGGGAACATGAACCTAACCTAACCTAAC	TAAATCTTYCNTAAATTGATHCCAT
<b>CIDR<math>\alpha</math>1.4</b>	AACTATCAAAATGGGAATGCTATT AACTATGAACAATGGAAATGCTATT AACTATCAAAATGGAATTGCTATT AACTATGAAAATGGCAATGCTATT AACAACTAAATGGAAATGCTATT	TTTCCCACTTATAGTGTCTATT TTTCCCACTTATAGTGTCTATT TTTCCCACTTATACTGTCTATT TTTCCCAGTTATAGTGTCTATT TTTCCCACCTATAGAGTCTATT
<b>CIDR<math>\alpha</math>1.5a</b>	GATTATGGATTAAGAATTATTAAG GATTGTGGGTACGAATTATTAAG GATTGTGGGTACATATTATTAAG	TAATTCATCCGTAAATTCTTCCA CAAATCTCCTTAAGTTTTCCA TAATTCATCCGTAAATTGATTCCA CAAATCTCCTTAAGTTTTCCA
<b>CIDR<math>\alpha</math>1.5b</b>	ACGATACTATAGACTGGAAATACG ATTGGGAWATAAACTTAAGACCTG TGGATACTACAGATTGGGATCGTA	AAACCCATTGTTCAAACACATTACA AAACCCATTATCAAAACACGTACA AAACCCATTATCAAAACACATACA
<b>CIDR<math>\alpha</math>1.6</b>	ATAATACTAATGTSACGGATTGT	CAGTTCTTATACTATCCCATTCC ACATCCTTATACTACCCCCATTCC AATTCTTATACTCTTCATTCTG
<b>CIDR<math>\alpha</math>1.7</b>	CGGAAACTATAACGTGGAACGATAA CGGAAACTATAAGGTGGAACGATAA CGGAAACTATAACGTGAAAGATAA GGATACTATAATGTGGAATGATAAA	TAGTTCTTATACTATTCCATTCC TAGTTCTTATACTATTCCATTCC TAGTTCTTATAATTATTCCATTCC TAGTTCTTATACTACTCCATTCC TAATTCTTATAATTATTCCATTCC
<b>CIDR<math>\alpha</math>1.8a</b>	ATAATTGTGAAATGAAAGGTTCA	TATGCAMTTCTTAAGTTGGTTCC
<b>CIDR<math>\alpha</math>1.8b</b>	AATAGACAGTATAATGTGGAA AAAGGATACTATAAAAGTGGGAA	CAAAACATWTACAATTTCGTTACA
DBL $\alpha$ 0.1	AGTAGAAWAGGTAAGGTGCGTA	CTATCCAATTTCATAACTATG
DBL $\alpha$ 0.16	ATATTYGAYTAYGTGCCRC	WKWTTCATACAKACGACACC
DBL $\alpha$ 0.6/9	GAAGGACAATCAATAACACAAGATTATC	CATAGTACATATTGAGAAGGAGA
DBL $\alpha$ 0.9	TTTCTSAAGTAMRTGGCGGTGAATGTG	AAATTTCTAACGCATAAATKTAATCG
CIDR $\alpha$ 2.2	ATGGTTCGATTATTGATATG	CCATCGTTATAACAWTCAC
CIDR $\alpha$ 2.3/5/6/7/9/10	TACARMATATTGYSAAAGCATGTCCG	TTTATCACCGGTAAAGTATTGGTAT
CIDR $\alpha$ 3.1-3	HWWMCAAAAGACATTCAATCC	TGTTCTCCARTRTATGGAATC
CIDR $\alpha$ 3.4	GAACCTGAKSAATTCCAAAAGACRT	CCTCTCCAATACATAGAATCGTTCAA
DBL $\beta$ 5	AACAYATGTGTACMTCNAATTAGAA	TAGCGWTTATTATCTCAKCTGCATC
ICAM-1 binding motif <sup>^</sup>	AATTNHTGCTNKAATGGGGTCTG	GGACCAAGTATGCCACCATTGTA

CIDR $\gamma$	SAWATGATTGATCGTAGGGGACC	TAAATGTAGTATAKTSATTRAGGTCTA
CIDR $\gamma$ 1/2	GATGAATTATGGGGATGTACTGR	AATTAAATTGTTATAAAAATCKC
CIDR $\gamma$ 2/9	GATGGTTAACAGATATTTTACASGATT	TCRYCTTCAACCACMTYTTGGGC
DBL $\epsilon$ 2	AAATTAAAGGTTGGRAGCACA	ACCATAATCTGCATAWGAYCTTTCAT
DBL $\epsilon$ 3	TGTATTGGTACCTCCTAGAAGA	TTAATCTTTAGCTTCAGAAAATGCMGAT
DBL $\epsilon$ 12	AATTACCTAACYGAAGATGAAATTCTCA	CTTTACATGCTGTTTGCCCATTCAA
DBL $\gamma$ DC9	ATTTACACGAWSAATTAVAAAAACTTGT	CTTTAGGTGGATWATCSAAAGCTTCAGG
DBL $\gamma$ 9	CCSAATTTSMGATYCATTGTT	RACMATATTCTTCCACCAS
DBL $\gamma$ DC6	AGACAAACCACAAACATCTGCTTCAG	TTAGGMGGAYAATCGAACGCTTCAGG
DBL $\zeta$ 4	ATWVNGAACCTCCTGATTATGAT	ATTCACCTCATTCTGCAAAAACGA
DBL $\zeta$ 5	ATATTACCAAAAGAAGGTGGATATAT	ATTCTCACAAWTTTCATCGWTTCC
DBL $\zeta$ 6	AWWVNGAWCCMCCTGATTATGA	TTCACTCCATTCTGCATCCAACG
DBL $\gamma$ DC5	GATTATGAKGGRTGTGAAAA	KYGTCTAGGTTTATGAGG
DBL $\beta$ 7 and DBL $\beta$ 9	AWGATTGGTGGGAAGCWAAYMGWG	CAAGAGGGTAACAGTGGTAGTATC
DBL $\alpha$ 1.5/6a	GATTAYGTCCCTCAATTTCAGWTGGT	GATTGTTTATTACAATCGTAACCCCTC
DBL $\alpha$ 1.5/6b	ATTGTAGTMRKGAGGGTTACGATTGTA	CWTYTKCACAAYKGGACAWTCTARATC
CIDR $\delta$	TAAATGTAACCTASATGTATGTGAA	AATACTYTAACCAACGTTAATMAATAC
DBL $\beta$ DC5	GTTGCTCCYMCCTTGTAAATGT CCCCCHCCYTTTGTAAAGTNCC TTGCACCCATTGGTAATATGCC	ACCACRTTGGTCGCATCTTGT CACTCACTATGTTGGTGYCATT GCCASCACTCWAUTCCNACCAC YACAYTWACCACATTNGTSGM
DBL $\alpha$ 1.5/6/8	GATTAYGTBCCTCAATTTCAGWTGGT	TTTTAGTACAATCATAACCACACCA GATTGTTTWTACAATCGTAACCCCTC ACAATCCTCACCATCACCACATACA CGTGATATATCTGTTKAGTACAATC GATCTGTTGTTACAATCGTAACCCCTC
CIDR $\delta$	TAAATGTAACCTAGATGTATGTGAA TAAATGTAACCTACATGTATGTGAA TAAATGTAACCTAGACGTATGTGAA TAAATGTTACTTAGATGTATGTGAA TAAATGTAACCTAGATATATGTGAA TAAATGTAAGITAGATGTATGTGAA	AATACTTAAACCAACGTTAATCAATAC AATACTTAAACCAACGCTTAATCAATAC AATACTGCAACCAACGTTAATCAATAC AATGCTCTAACCAACGTTAATGAATAC AATACATCAACCAACGCTTAATCAATAC AATATTCTAACCAACCGTTAAATAGTAC
DBL $\alpha$ 1.1	TTGATGAAGATGAAGAACATCTGAATG	GAGCTCCAAGTTTATCACACAT
DBL $\epsilon$ 8	AAGAGGATCTACTTAATGCTGCTTTAG	AACTGAACCTCATAGCCTCATATGC
VarA	TTGGGRAATBTGTTAGTTAYRGCAA	CTGCAAAACTKCGWGCAAG
UpsB1	CATCCGCCATGCAAGTATAA	CGTGCACGATTGATTTGATT
UpsC1	CACATCGATTACATTAGCGTTT	TGTGGTAATATCATGTAATGG

<sup>a</sup>Primers from Lennartz et al. 2017; Group primers from Rottmann et al. 2006.

Remaining domain primers from Lavstsen et al. 2012, Petersen et al. 2016/Mkumbaye et al. 2017 (**bold**).

Table S4. var domain expression levels in Ret+CM, Ret-CM, and UM cases, Related to Figures 2 and 3

Binding phenotype/Domain classification	Primer/Domain subclass	DC	Group	Ret+CM (n = 49)	Ret-CM (n = 18)	P-value*	FDR*	UM (n = 38)	P-value*	FDR*	
EPCR	DBLα2α1.1/2/4/7	B/A, A	143.1 [75.4, 231.7]	89.8 [37.9, 246.0]	0.28	0.80	32.0 [8.9, 76.2]	<0.0001	<0.0001		
	DBLα1.4	A	1.4 [1, 6.9]	1 [1, 4.3]	0.75	0.95	1 [1, 1.4]	0.02	0.03		
	CIDRα1.4 and CIDRα1	A	10.0 [1.3, 20.0]	7.6 [1.4, 25.7]	0.76	0.95	2.1 [1, 6.5]	0.002	0.004		
	CIDRα1.6	A	1 [1, 3.4]	1 [1, 1.7]	0.42	0.82	1 [1, 1]	0.10	0.13		
	CIDRα1.7	A	9.5 [1.9, 32.9]	2.1 [1, 19.2]	0.15	0.80	1 [1, 5.4]	0.0001	0.0004		
	DBLβ3	A	10.6 [5.2, 43.1]	4.1 [1.2, 43.5]	0.28	0.80	1.3 [1, 10.4]	0.0001	0.0004		
	DBLα-CIDRα	8	B/A	10.6 [2.3, 30.6]	10.4 [4.1, 34.8]	0.87	0.96	1.8 [1, 9.5]	0.0003	0.0009	
	CIDRα1.1	8	B/A	27.5 [3.9, 103.7]	22.6 [1, 85.5]	0.49	0.82	5.3 [1, 30.0]	0.003	0.006	
	DBLβ12 and DBLβ3/5	8	B/A,A	32.0 [11.3, 63.7]	55.0 [16.3, 103.7]	0.40	0.82	11.6 [4.1, 24.2]	0.0005	0.001	
	DBLγ4/6	8	B/A	37.2 [16.0, 95.3]	29.5 [6.8, 98.6]	0.50	0.82	12.8 [2.3, 35.9]	0.009	0.02	
	DBLα1.7	13	A	37.1 [6.4, 75.1]	10.5 [1.2, 35.2]	0.18	0.80	2.1 [1, 16.2]	0.0001	0.0004	
	CIDRα1.4	13	A	2.3 [1, 5.6]	1.8 [1, 6.3]	0.91	0.96	1 [1, 1]	0.0002	0.0007	
CD36	Total CIDRα1	A, B/A	132.7 [74.6, 292.7]	117.1 [39.3, 401.6]	0.55	0.88	24.7 [7.0, 41.6]	<0.0001	<0.0001		
	DC8 CIDRα1.1/8	8	B/A	46.2 [9.9, 97.4]	36.6 [17.0, 114.8]	0.80	0.95	9.6 [1.6, 28.6]	0.002	0.004	
	Group A CIDRα1.4-7	A	82.0 [36.1, 170.0]	49.0 [12.2, 196.4]	0.28	0.80	8.4 [1, 31.4]	<0.0001	<0.0001		
	CIDRα1.1	8	B/A	36.2 [5.8, 79.8]	22.3 [7.3, 72.7]	0.92	0.96	4.5 [1, 26.3]	0.002	0.005	
	CIDRα1.4	13	A	3.5 [1, 9.4]	4.9 [1, 8.1]	0.67	0.95	1 [1, 3.4]	0.005	0.009	
	CIDRα1.5	A	24.4 [5.3, 60.5]	7.2 [3.6, 43.3]	0.41	0.82	1 [1, 8.6]	<0.0001	<0.0001		
	CIDRα1.6	A	6.9 [1.1, 23.4]	4.9 [1, 16.1]	0.35	0.82	1 [1, 3.1]	<0.0001	<0.0001		
	CIDRα1.7	A	17.8 [3.4, 47.7]	5.4 [1, 16.8]	0.16	0.80	1.2 [1, 12.0]	0.0001	0.0004		
	CIDRα1.8	8	B/A	4.9 [1, 17.5]	5.3 [1, 11.0]	0.81	0.95	1.3 [1, 3.7]	0.04	0.06	
	DBLα0.1	B	1 [1, 1.3]	1 [1, 3.9]	0.19	0.80	1 [1, 1]	0.02	0.03		
ICAM-1	DBLα0.16	19	B	6.0 [1.2, 23.0]	15.4 [2.0, 30.0]	0.24	0.80	3.4 [1, 13.8]	0.35	0.38	
	DBLα0.6/9	B	2.1 [1, 7.8]	7.6 [2.0, 25.5]	0.03	0.42	1 [1, 3.0]	0.16	0.19		
	DBLα0.9	20	B	6.1 [1.4, 13.8]	6.4 [1.2, 25.4]	0.73	0.95	3.6 [1, 9.5]	0.07	0.10	
	CIDRα2.2	B	3.9 [1, 11.4]	2.4 [1, 10.9]	0.50	0.82	1.1 [1, 2.8]	0.02	0.03		
	CIDRα2.3/5/6/7/9/10	B	15.3 [7.4, 42.7]	27.4 [5.3, 48.0]	0.79	0.95	19.1 [6.6, 30.2]	0.56	0.57		
	CIDRα3.1-3	B,C	3.6 [1, 11.3]	5.3 [1.1, 11.9]	0.74	0.95	3.1 [1, 4.8]	0.23	0.26		
	CIDRα3.4	19	B,C	9.8 [3.3, 28.1]	23.2 [1.6, 47.8]	0.37	0.82	5.1 [1, 16.1]	0.08	0.11	
	DBLβ5	B (A,C)	1.1 [1, 4.5]	2.7 [1, 7.3]	0.39	0.82	1 [1, 2.0]	0.07	0.10		
	ICAM-1 binding motif <sup>a</sup>	A	17.1 [7.1, 32.7]	15.9 [3.8, 41.6]	0.61	0.92	1.7 [1, 12.8]	<0.0001	<0.0001		
	CIDRγ	B,C	8.0 [3.3, 22.9]	14.1 [4.3, 43.7]	0.45	0.82	7.8 [2.4, 19.4]	0.44	0.47		
C-terminal DBL	CIDRγ1/2	B	5.8 [2.4, 12.5]	8.0 [1, 23.4]	0.41	0.82	5.5 [1.6, 9.8]	0.53	0.55		
	CIDRγ2/9	B	2.3 [1, 11.5]	2.8 [1, 21.3]	0.77	0.95	1.3 [1, 8.1]	0.27	0.30		
	DBLε2	7	B (C)	9.4 [3.7, 48.0]	1.1 [1, 18.9]	0.01	0.42	1 [1, 3.5]	<0.0001	<0.0001	
	DBLε3	7	B (A,C)	1.9 [1, 6.6]	1.2 [1, 6.8]	0.93	0.96	1 [1, 4.4]	0.21	0.24	
	DBLε12	12	B,A	1 [1, 1]	1 [1, 1]	0.76	0.95	1 [1, 1]	0.12	0.15	
	DBLγ	9	B	8.8 [3.0, 44.0]	9.9 [3.3, 32.6]	0.98	0.98	5.1 [1, 9.9]	0.007	0.01	
	DBLγ9	9	A,B,C	1 [1, 1.9]	1 [1, 1.7]	0.92	0.96	1 [1, 1.2]	0.50	0.53	
	DBLγ	6	B (A,C)	15.2 [1.3, 69.3]	24.7 [6.8, 64.3]	0.43	0.82	3.9 [1, 20.5]	0.03	0.05	
	DBLζ4	9	B	3.9 [1.7, 12.0]	3.9 [1.1, 16.4]	0.87	0.96	2.4 [1, 5.9]	0.07	0.10	
	DBLζ5	6	B (A,C)	2.0 [1, 11.9]	5.4 [1, 24.1]	0.30	0.80	1 [1, 5.5]	0.14	0.17	
Group A - Unknown	DBLζ6	10	B	1.5 [1, 4.3]	1 [1, 6.7]	0.60	0.92	1 [1, 1.9]	0.02	0.03	
	DBLγ	5	A	2.5 [1, 10.6]	1 [1, 2.8]	0.06	0.49	1 [1, 2.2]	0.002	0.004	
	DBLβ7 and DBLβ9	5	A	1.3 [1, 5.7]	1 [1, 10.7]	0.66	0.95	1 [1, 1]	0.006	0.01	
	DBLα1.5/6a	16	A	24.7 [3.4, 91.9]	7.8 [1, 30.2]	0.11	0.68	2.7 [1, 23.1]	0.001	0.004	
	DBLα1.5/6b	16	A	9.3 [2.3, 36.2]	2.4 [1, 9.8]	0.04	0.45	1.8 [1, 9.5]	0.002	0.004	
	CIDRδ	16	A	5.7 [1.1, 15.9]	1.2 [1, 5.5]	0.07	0.49	1 [1, 2.0]	0.0001	0.0004	
	DBLβ	5	A	11.6 [5.8, 49.4]	5.6 [1.4, 18.5]	0.07	0.49	ND	ND	ND	
	DBLα1.5/6/8	16	A	61.4 [1, 223.2]	16.3 [1, 70.7]	0.21	0.80	27.8 [10.8, 60.2]	0.10	0.13	
	CIDRδ	16	A	12.9 [1.5, 36.8]	3.2 [1, 9.4]	0.03	0.42	1.1 [1, 3.9]	0.0004	0.0004	
	Unknown phenotype	DBLα1.1	1	A	4.0 [1, 12.1]	2.6 [1.1, 11.7]	0.94	0.96	1.7 [1, 3.4]	0.01	0.02
Group	VarA			102.6 [64.3, 153.0]	78.6 [15.0, 208.7]	0.30	0.80	26.4 [2.9, 66.3]	<0.0001	<0.0001	
	UpsB1			24.4 [9.1, 45.3]	30.6 [13.5, 69.1]	0.50	0.82	12.6 [1.9, 28.4]	0.002	0.004	
	UpsC1			7.6 [3.0, 12.4]	2.9 [1, 5.1]	0.02	0.42	1.9 [1, 4.1]	<0.0001	<0.0001	

Values listed as median [25th, 75th]; \*P-values correspond to Wilcoxon rank-sum test between indicated group and Ret+CM. FDR\*, Simes adjustment for multiple comparisons/false discovery rate

<sup>a</sup>Primers from Lennartz et al. 2017; Remaining domain primers from Lavstsen et al. 2012 (white), Petersen et al. 2016 (grey), Mukumbaye et al. 2017 (grey).

Group primers from Rottmann et al. 2006. ND, not determined. Total CIDRα1, sum of CIDRα1.1/4/5/6/7/8; DC8 CIDRα1.8, sum of CIDRα1.1/4/5/6/7.

Table S5. var domain expression levels in CM cases by brain swelling severity, Related to Figure 3

Binding phenotype/Domain classification	Primer/Domain subclass	DC	Group	Absent (n = 18)	Mild/moderate (n = 17)	P-value*	FDR*	Severe (n = 22)	P-value*	FDR*
EPCR	DBLα2/α1.1/2/4/7	B/A, A	171.6 [61.2, 249.9]	122.6 [91.5, 220.1]	0.84	0.97	133.5 [69.0, 214.5]	0.62	0.93	
	DBLα1.4	A	1 [1, 4.3]	1 [1, 9.8]	0.68	0.97	3.6 [1, 7.3]	0.20	0.93	
	CIDRα1.4 and CIDRα1	A	4.3 [1, 11.0]	15.3 [10.4, 21.5]	<b>0.04</b>	0.70	9.7 [4.3, 30.9]	0.25	0.93	
	CIDRα1.6	A	1 [1, 2.3]	1 [1, 6.2]	0.32	0.75	1 [1, 1.1]	0.56	0.93	
	CIDRα1.7	A	5.6 [1, 75.8]	13.0 [3.3, 26.8]	0.55	0.96	15.5 [4.6, 43.3]	0.49	0.93	
	DBLβ3	A	15.4 [1.2, 45.5]	17.1 [9.5, 62.9]	0.32	0.75	8.0 [3.9, 44.0]	0.96	0.98	
	DBLα-CIDRα	8	B/A	10.1 [2.1, 24.8]	30.6 [9.1, 48.3]	<b>0.03</b>	0.70	10.4 [4.0, 25.0]	0.68	0.93
	CIDRα1.1	8	B/A	35.8 [3.2, 116.4]	31.0 [2.4, 85.5]	0.94	0.97	30.4 [8.8, 108.8]	0.74	0.93
	DBLβ12 and DBLβ3/5	8	B/A,A	56.7 [17.7, 76.4]	56.1 [29.1, 79.4]	0.64	0.97	19.4 [6.7, 88.8]	0.29	0.93
	DBLγ4/6	8	B/A	46.8 [15.3, 95.3]	62.6 [22.8, 98.6]	0.64	0.97	35.5 [18.8, 98.5]	0.93	0.98
	DBLα1.7	13	A	21.1 [8.0, 100.2]	39.2 [2.7, 110.0]	0.96	0.97	32.0 [11.6, 58.0]	0.75	0.93
	CIDRα1.4	13	A	1.7 [1, 6.8]	3.0 [1.5, 7.2]	0.29	0.75	2.2 [1, 4.6]	0.87	0.94
	<b>Total CIDRα1</b>	A, B/A	132.7 [98.1, 251.6]	188.3 [68.6, 390.1]	0.88	0.97	167.2 [89.5, 404.6]	0.82	0.94	
	<b>DC8 CIDRα1.1/8</b>	8	B/A	46.2 [34.3, 85.3]	88.9 [9.1, 140.9]	0.84	0.97	54.1 [11.3, 157.9]	0.63	0.93
	<b>Group A CIDRα1.4-7</b>	A	81.4 [37.8, 164.2]	88.7 [42.6, 228.6]	0.58	0.96	91.6 [33.4, 186.5]	0.79	0.94	
	CIDRα1.1	8	B/A	38.2 [9.6, 68.5]	34.1 [3.4, 98.5]	0.97	0.97	50.5 [10.7, 91.7]	0.61	0.93
	CIDRα1.4	13	A	4.3 [1.9, 7.9]	7.6 [1, 20.6]	0.30	0.75	3.3 [1, 5.6]	0.52	0.93
	CIDRα1.5	A	28.4 [9.3, 62.5]	24.9 [3.4, 83.4]	0.97	0.97	24.5 [15.4, 46.9]	0.76	0.93	
	CIDRα1.6b	A	7.8 [1, 39.3]	15.7 [1.7, 28.1]	0.71	0.97	5.6 [2.1, 10.9]	0.72	0.93	
	CIDRα1.7	A	10.5 [1, 39.9]	9.1 [3.9, 96.4]	0.40	0.78	38.4 [6.9, 47.7]	0.15	0.93	
	CIDRα1.8	8	B/A	5.5 [1, 18.1]	12.2 [6.8, 55.8]	<b>0.02</b>	0.70	1.6 [1, 9.4]	0.34	0.93
CD36	DBLα0.1	B	1.1 [1, 3.0]	1 [1, 1]	0.13	0.75	1 [1, 1.3]	0.29	0.93	
	DBLα0.16	19	B	15.4 [2.6, 30.0]	11.6 [2.0, 24.7]	0.82	0.97	4.7 [1.1, 11.3]	0.08	0.93
	DBLα0.6/9	B	2.4 [1, 7.0]	2.3 [1, 7.8]	0.86	0.97	5.3 [1.7, 13.3]	0.22	0.93	
	DBLα0.9	20	B	15.9 [5.2, 27.9]	6.1 [3.0, 12.1]	0.12	0.75	5.9 [1.5, 13.4]	0.15	0.93
	CIDRα2.2	B	2.4 [1, 15.7]	4.1 [1.1, 11.4]	0.78	0.97	4.7 [1.2, 10.1]	0.70	0.93	
	CIDRα2.3/5/6/7/9/10	B	11.1 [5.6, 48.0]	18.1 [6.7, 31.2]	0.95	0.97	29.1 [14.5, 50.6]	0.19	0.93	
	CIDRα3.1-3	B,C	6.3 [1, 10.2]	2.3 [1, 5.7]	0.33	0.75	7.0 [1.4, 17.7]	0.50	0.93	
	CIDRα3.4	19	B,C	21.2 [6.6, 35.9]	13.9 [6.6, 30.2]	0.96	0.97	10.4 [2.1, 31.8]	0.41	0.93
	DBLβ5	B (A,C)	1 [1, 2.4]	1.4 [1, 5.2]	0.61	0.97	2.7 [1.1, 8.7]	0.07	0.93	
	ICAM-1 binding motif <sup>a</sup>	A	16.3 [2.2, 37.1]	18.0 [14.0, 72.0]	0.31	0.75	22.9 [7.1, 44.7]	0.61	0.93	
ICAM-1	CIDR $\gamma$	B,C	11.1 [6.7, 53.3]	6.9 [5.5, 16.8]	0.32	0.75	11.1 [2.3, 24.5]	0.51	0.93	
	CIDR $\gamma$ 1/2	B	7.0 [1.8, 24.1]	6.8 [1.8, 14.9]	0.84	0.97	9.0 [3.2, 14.7]	0.87	0.94	
C-terminal DBL	CIDR $\gamma$ 2/9	B	4.1 [1, 25.6]	3.1 [1.4, 21.3]	0.92	0.97	3.0 [1, 9.3]	0.31	0.93	
	DBL $\epsilon$ 2	7	B (C)	26.9 [3.2, 62.7]	4.6 [1, 38.1]	0.35	0.75	6.5 [3.8, 44.6]	0.63	0.93
	DBL $\epsilon$ 3	7	B (A,C)	1.4 [1, 4.4]	3.6 [1, 7.9]	0.27	0.75	1.8 [1, 9.5]	0.54	0.93
	DBL $\epsilon$ 12	12	B,A	1 [1, 2.9]	1 [1, 1]	0.11	0.75	1 [1, 1.3]	0.57	0.93
	DBL $\gamma$	9	B	20.1 [2.8, 66.8]	6.7 [2.1, 32.6]	0.41	0.78	10.9 [4.1, 40.1]	0.34	0.93
	DBL $\gamma$ 9	9	A,B,C	1 [1, 1.2]	1.6 [1, 3.5]	0.13	0.75	1 [1, 1.6]	0.95	0.98
	DBL $\gamma$ 6	6	B (A,C)	26.3 [1.1, 91.8]	24.7 [4.6, 69.3]	0.89	0.97	26.8 [3.3, 62.6]	0.73	0.93
	DBL $\zeta$ 4	9	B	9.3 [2.5, 16.4]	2.6 [1.3, 12.6]	0.28	0.75	6.6 [2.4, 13.1]	0.61	0.93
	DBL $\zeta$ 5	6	B (A,C)	2.0 [1, 19.1]	1.2 [1, 11.9]	0.89	0.97	5.0 [1.5, 14.8]	0.46	0.93
	DBL $\zeta$ 6	10	B	1.4 [1, 4.0]	3.3 [1, 8.9]	0.34	0.75	1.7 [1, 3.5]	0.51	0.93
Group A - Unknown	DBL $\gamma$ 5	5	A	1 [1, 2.4]	4.5 [1, 16.3]	<b>0.05</b>	0.70	3.6 [1.3, 14.2]	<b>0.03</b>	0.93
	DBL $\beta$ 7 and DBL $\beta$ 9	5	A	2.2 [1, 11.5]	1.4 [1, 10.4]	0.68	0.97	1.9 [1, 4.0]	0.41	0.93
	DBL $\alpha$ 1.5/6a	16	A	25.9 [1, 55.1]	46.3 [12.9, 79.2]	0.19	0.75	23.5 [4.8, 105.2]	0.59	0.93
	DBL $\alpha$ 1.5/6b	16	A	7.8 [1, 32.5]	12.8 [5.5, 34.9]	0.24	0.75	7.6 [2.0, 42.8]	0.62	0.93
	CIDR $\delta$	16	A	4.0 [1, 10.6]	7.7 [2.2, 22.8]	0.42	0.78	3.5 [1, 17.2]	0.87	0.94
	DBL $\beta$	5	A	20.5 [8.3, 47.3]	10.3 [4.7, 20.1]	0.19	0.75	27.3 [7.9, 60.3]	0.99	0.99
	DBL $\alpha$ 1.5/6/8	16	A	28.8 [1, 130.1]	89.4 [30.1, 261.4]	0.21	0.75	60.0 [1, 157.7]	0.65	0.93
	CIDR $\delta$	16	A	10.5 [1, 25.3]	17.5 [3.6, 34.1]	0.42	0.78	12.2 [2.2, 36.8]	0.53	0.93
	DBL $\alpha$ 1.1	1	A	3.4 [1.2, 8.3]	1.1 [1, 13.2]	0.58	0.96	6.4 [1, 13.5]	0.56	0.93
	DBL $\epsilon$ 8	3	A	6.1 [1, 16.6]	13.1 [2.7, 42.4]	0.20	0.75	2.5 [1, 8.4]	0.29	0.93
Unknown phenotype	VarA			135.1 [77.4, 193.5]	106.7 [82.2, 143.9]	0.53	0.96	94.6 [55.5, 179.1]	0.45	0.93
	UpsB1			32.6 [20.0, 70.4]	21.5 [12.7, 39.8]	0.28	0.75	26.2 [10.9, 44.4]	0.36	0.93
	UpsC1			7.6 [3.0, 14.7]	5.1 [1.5, 9.8]	0.20	0.75	7.4 [3.8, 13.4]	0.85	0.94

Values listed as median [25th, 75th]; \*P-values correspond to Wilcoxon rank-sum test between indicated group and Absent. FDR\*, Simes adjustment for multiple comparisons/false discovery rate

<sup>a</sup>Primers from Lennartz et al. 2017; Remaining domain primers from Lavstsen et al. 2012 (white), Petersen et al. 2016 (grey), Mkumbaye et al. 2017 (grey); Group primers from Rottmann et al. 2004

Total CIDRα1, sum of CIDRα1.1/4/5/6/7/8; DC8 CIDRα1.1/8, sum of CIDRα1.1/8; Group A CIDRα1.4-7, sum of CIDRα1.4/5/6/7

Table S6: Primer grouping for Random Forest set enrichment analysis, Related to Figure 4

Lavstsen et al., 2012, Petersen et al., 2016, Mikumbaye et al., 2017, Lennartz et al., 2017

EPCR binders	CIDRa1 domains	Group A	DC8	CD36 binders	Group A- Unknown	DC5	DC16	ICAM-1 binders	IgM binders
DBLα2/1 1/2/4/7	CIDRa1.4 2016	DC13	DBLα1.1	DC1	DBLα/CIDRa1	DC19	DBLα and DBLβ9	DBLβ3	DBLy
DBLα1.4	CIDRa1.6 2016		DBLα0	DC3	CIDRa1.1 2016	DC19	DBLα2	DBLβ5	DC6
DBLα1.7	DC13	CIDRa1.6b 2016	DBLα0.1/2/4/7		CIDRa1.8 2016	DC20	DBLγ 2016	DBL2	DC6
CIDRa1.4 2016	DC13	CIDRa1.7 2016	DBLα1.4		DBLβ12 and DBLβ3/5	DC16	DBLα1.5/6/8 2016	DBL3	DC7
CIDRa1.5 2016		CIDRa1.1 2016	DBLα1.7	DC13	DBLα0.1	DC16	CIDRa6 2016	DBL4	DC7
CIDRa1.6b 2016		CIDRa1.8 2016	DBLα4/6	DC13	DBLα0.6/9			DBL12	DC12
CIDRa1.7 2016					CIDRa2.2				
CIDRa1.4 and CIDRa1					CIDRa2.3,5,6,7,9,10				
DBLα2	DC8				CIDRa3.1/3				
CIDRa1.1 2016	DC8				DBLα8				
CIDRa1.8 2016	DC8				DBLα2	DC7			
DBLα12 and DBLβ3/5	DC8				DBLα3	DC7			
DBLγ4/6	DC8				DBLβ7 and DBLβ9	DC5			
DBLβ3					DBLγ 2016	DC5			
ICAM-1 binding motif					DBLα1.5/6/8 2016	DC16			
					CIDR6	DC16			
					VarA				
					ICAM-1 binding motif				

**Table S8. Number of unique DBL $\alpha$  tags per patient, Related to Figure 5**

Patient ID <sup>a</sup>	# Reads <sup>b</sup>	# Unique DBL $\alpha$ Tags	
		75% Population	90% Population
3320	624,674	10	34
3321	526,648	11	21
3323	436,764	10	24
3327	488,279	16	46
3329	559,208	12	26
3340	587,067	15	31
3344	571,053	13	44
3352	408,909	18	52
3366	557,837	5	18
3373	441,941	7	23
3361	467,674	4	11
3342	476,982	2	3
3374	539,338	11	25

<sup>a</sup>Colored by brain swelling status; red: severe swelling, orange: moderate swelling, black: no swelling.

<sup>b</sup>Illumina MiSeq sequencing reads

**Table S9. Summary of identical DBL $\alpha$  tags in/between 2015-2016 isolates and 1999-2003 brain samples, Related to Figure 5**

Common DBL $\alpha$ Tags			
Tag	2015-2016 Cohort <sup>a</sup>	1999-2003 Brain Samples <sup>b</sup>	Predicted PfEMP1 type (BLAST) <sup>c</sup>
1	3320-28 <sup>d</sup> , 3340-30, 3373-12	78B1-8_KC678520	GrpB/C
2	3321-3, 3323-22	79B1-2.03_KC678564	GrpA-EPCR
3	3321-11	78B1-18_KC678522	GrpA-EPCR
4	3327-11	34E3-35_KC678168	GrpB/C
5	3344-7	37B1-2.50_KC678223	GrpA-EPCR
6	3352-33	82F3-2.03_KC678616	var1csa
7	3352-41	61B1-15_KC678299	GrpA-EPCR
8	3366-4	75B-1-11_KC678489	GrpB/C
9	3320-11, 3327-7, 3329-5, 3344-16, 3373-4	--	var1csa
10	3361-7, 3340-29, 3366-15	--	var1csa
11	3320-1, 3327-15	--	GrpA-EPCR
12	3320-3, 3323-13	--	DC8
13	3320-10, 3352-24	--	var1csa
14	3321-2, 3373-22	--	Ambiguous
15	3323-5, 3344-15	--	GrpB/C
16	3323-9, 3352-14	--	GrpA-EPCR
17	3327-43, 3352-16	--	GrpB/C
18	3327-28, 3344-1	--	GrpA-EPCR
19	3344-34, 3361-3	--	GrpA-EPCR
20	3352-32, 3366-8	--	GrpB/C
21	3374-10, 3344-11	--	GrpB/C

<sup>a</sup>Colored by brain swelling status; red: severe swelling, orange: moderate swelling, black: no swelling.

<sup>b</sup>Tembo et al. 2014

<sup>c</sup>Prediction based on top 5 BLAST hits. Dark color: ≥4 of the top 5 hits were of the same type. Light color: 3 of the top 5 hits were of the same type. Ambiguous: <3 were of the same type. See also Figure S4 and Table S7.

<sup>d</sup>Patient ID-Tag #